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Original Research Article

Salivary uric acid as a non-invasive marker of early onset preeclampsia

Shaily Agarwal, Divya Dwivedi, Renu Gupta, Garima Gupta, Pavika Lal, Neha*

Department of Obstetrics and Gynecology, GSVM Medical College, Kanpur, Uttar Pradesh, India

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***Correspondence:**
Dr. Neha,
E-mail: neha.swayam04@gmail.com

ABSTRACT

Background: Preeclampsia is one of the most common complications in pregnancy and is a major cause of maternal and perinatal morbidity and mortality. Early prediction of preeclampsia is crucial in proactive management of the patient. Uric acid is a biomarker of hypertension.
Methods: A prospective study was done on 200 pregnant females in their first or early second trimester of pregnancy and were followed till one week of delivery or termination of pregnancy. After taking socio-demographic details, detailed medical and obstetric history was taken. Blood pressure of the patients was routinely measured and mean arterial pressure was calculated. Blood and saliva samples were taken and were analysed following standard protocol for serum and salivary uric acid levels respectively. Participants were classified into normotensive and preeclampsia groups depending on the criteria met.
Results: Preeclampsia group participants had significantly more adverse and feto-maternal outcomes. Salivary uric acid is a promising diagnostic predictor of preeclampsia in pregnant women by the virtue of being a non-invasive investigation with cut off value 4.86 mg/dl having a sensitivity of 70.8%, specificity of 45.7% and a PPV of 81.3%. Salivary uric acid level and mean arterial pressure were found to be better predictors of preeclampsia as compared to salivary uric acid level.
Conclusions: Salivary uric acid is a reliable predictor of preeclampsia in pregnant females in first and early second trimester of pregnancy. Further largescale studies are warranted to establish an accurate cut off value with good diagnostic properties for Indian population.

Keywords: Feto-maternal outcome, Preeclampsia, Salivary uric acid, Serum uric acid

INTRODUCTION

Preeclampsia is one of the most common complications during pregnancy. It is marked by hypertension accompanied by hyperuricemia. As per ICD-10, preeclampsia (PE) is diagnosed when a normotensive women develops hypertension (systolic BP >140 mm Hg and diastolic BP ≥90 mm Hg) after 20 weeks of gestation with proteinuria (≥30 mg/dl or ≥1+ on dipstick).[1-3] It is a multisystem disorder that is a major source of maternal and perinatal morbidity and mortality. Nearly 10-15% of maternal deaths worldwide are directly attributed to preeclampsia and eclampsia.[2] Uric acid has been found to be a biomarker of a number of metabolic disorders as well as hypertension.[4] Serum uric acid has been found to be a reliable predictor of preeclampsia in a number of studies.[5-7] Serum analysis for uric acid is an invasive procedure. Some studies have explored salivary uric acid level as a predictor of preeclampsia as the method is non-invasive.[4,8,9] A reliable and universally accepted cut off level of salivary uric acid has not been yet established.

METHODS

The current prospective observational study was done at the department of obstetrics and gynaecology at a tertiary care hospital in Kanpur, India over a period of two years.

Pregnant women attending outpatient clinic at the hospital were recruited in the study.

Inclusion criteria

All pregnant women aged 18 to 45 years, in their first or early second trimester of pregnancy who gave consent to participate and were willing to follow up were recruited.

Exclusion criteria

Patients with a history of renal disease or chronic hypertension were excluded. Patients with multiple gestation were also excluded.

200 participants meeting the inclusion and exclusion criteria were recruited. Detailed medical and obstetric history was taken along with socio-demographic details of the patients. Gestational age was determined using ultrasonography to ascertain gestational age and number of foetus. Blood pressure was measured and mean arterial pressure (MAP) was calculated. Blood sample was analysed for serum uric acid (serum UA) level. Saliva sample was collected by passive drooling and was analysed for salivary uric acid (salivary UA) concentration. The patients were followed till one week after delivery or termination of pregnancy. Depending on whether the patient met the criteria for preeclampsia, the sample was divided into two groups, namely preeclampsia group and normotensive group.

Statistical analysis

The data so obtained was coded, anonymized and analysed for correlations and significance by suitable statistical techniques using IBM SPSS version 23. Receiver operator characteristic (ROC) curve was plotted for serum UA level and salivary UA level data. The curves were then analysed for area under the curve (AUC) and cut off values for prediction of preeclampsia.

RESULTS

The socio-demographic details of the participants have been summarised in Table 1. As per the ICD-10 criteria for preeclampsia, 154 of 200 participants were normotensive while 46 developed preeclampsia. The participants fell in the age range of 19-42 years. Majority of the participants were educated till high school and belonged to middle socio-economic status. Around 80 percent of the participants in both the groups were gravida 1 or 2.

Table 1: Socio-demographic details of the participants.

Variables		Groups	
		Normotensive group	Preeclampsia group
Number of participants	N	154 (77.0%)	46 (23.0%)
Age	Mean±SD (years)	26.7±4.28	28.54±4.82
Education	Illiterate	1 (0.65%)	1 (2.17%)
	Primary	33 (21.43%)	17 (36.96%)
	High school	102 (66.23%)	24 (52.17%)
	Graduate	18 (11.69%)	4 (8.70%)
Socio-economic status	Low	20 (12.99%)	12 (26.09%)
	Middle	132 (85.71%)	34 (73.91%)
	Higher	2 (1.30%)	0 (0%)
Gravidity	Gravida 1	65 (42.21%)	17 (36.96%)
	Gravida 2	63 (40.91%)	19 (41.30%)
	Gravida 3	21 (13.64%)	6 (13.04%)
	Gravida 4	5 (3.24%)	4 (8.70%)

Table 2: Comparison of serum UA, salivary UA, and mean arterial pressure (MAP).

	Normotensive group (n=154)		Preeclampsia group (n=46)		t	P value
	Mean	±SD	Mean	±SD		
MAP (mmHg)	86.85	8.86	115.14	13.51	-16.66	<0.001*
Serum UA	4.61	1.88	6.35	2.48	-5.10	<0.001*
Salivary UA	3.79	2.91	4.97	3.48	-2.29	0.023*

Table 2 summarises the comparison of the measures of MAP, serum UA and salivary UA between the normotensive and the preeclampsia group. When the entire sample was taken as a single group, the serum UA had a significant Pearson's correlation coefficient of 0.706 (p=0.000). The preeclampsia group had significantly higher MAP as compared to the normotensive group (p<0.001). The mean serum UA and mean salivary UA were found to be significantly higher in the preeclampsia

group. Mean salivary UA was lower than corresponding mean serum UA in both the groups.

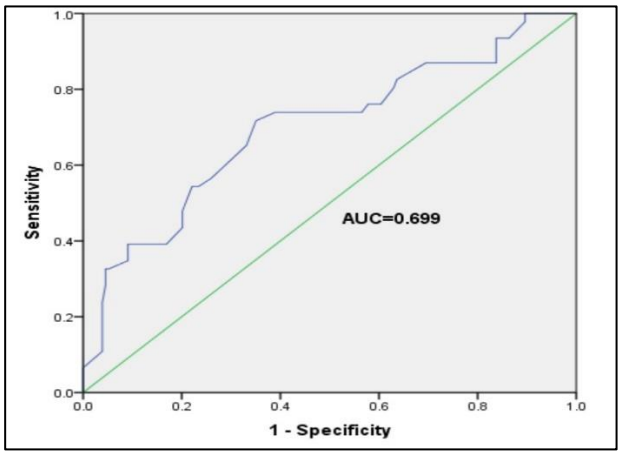

Figure 1: Receiver operating characteristic curve of serum UA.

Figure 1 depicts the ROC curve for serum UA. The AUC obtained was 0.699 with corresponding cut off value of 5.18 mg/dl having a sensitivity of 66.2%, specificity of 71.7%, positive predictive value (PPV) of 88.7% and negative predictive value (NPV) of 38.8% (Table 3). Figure 2 shows the ROC curve for salivary UA. The AUC came out to be 0.591. The cut off value obtained was 4.86 mg/dl. The corresponding sensitivity, specificity, PPV ad NPV are 70.8%, 45.7%, 81.3% and 31.8% respectively (Table 3).

Table 3: Comparison of predictive values of serum UA, salivary UA, pulsatility index (PI) and mean arterial pressure (MAP).

	Serum UA	Salivary UA	MAP
Cut off value	5.18 mg/dl	4.86 mg/dl	100 mmHg
Sensitivity (%)	66.2	70.8	95.7
Specificity (%)	71.7	45.7	94.2
PPV (%)	88.7	81.3	83.0
NPV (%)	38.8	31.8	98.6

The ROC curve of MAP has been depicted in Figure 3. The AUC came out to be 0.966 and cut off value was determined to be 100 mm Hg. For this cut off value of MAP, the corresponding sensitivity, specificity, PPV ad NPV are 95.7%, 94.2%, 83.0% and 98.6% respectively (Table 3).

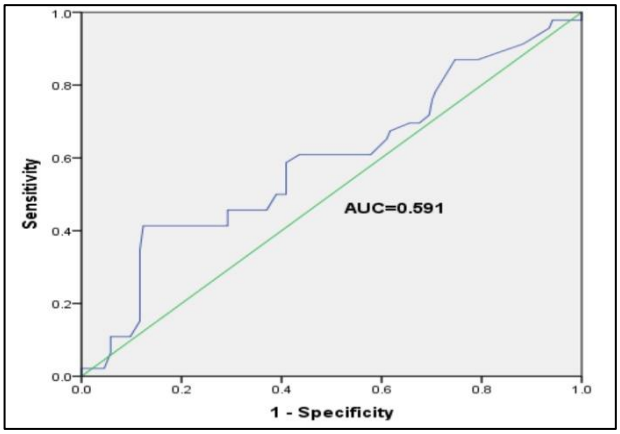

Figure 2: Receiver operating characteristic curve of salivary UA.

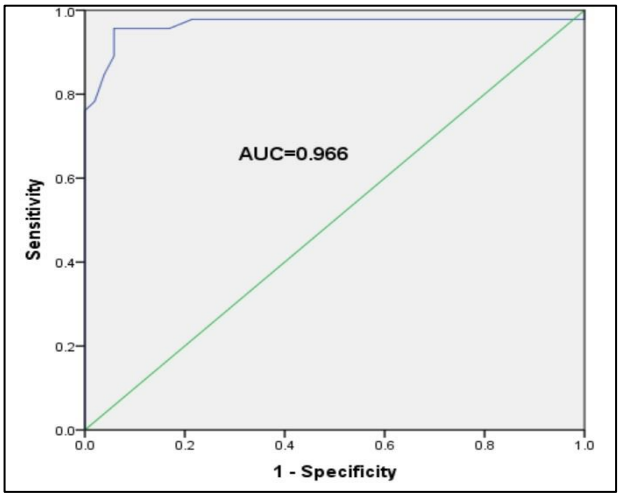

Figure 3: Receiver operating characteristic curve of mean arterial pressure (MAP).

Table 4: Distribution of participant according to different fetal measures in between groups.

		Normotensive group (n=154)		Preeclampsia group (n=46)		Chi square	P value
		n	**%**	**n**	**%**		
Fetal outcome	Stable	150	97.40	34	73.91	32.200	0.000*
	IUFD	4	2.60	4	8.70		
	NICU admission	0	0.00	8	17.39		
Birth	Term	137	91.3	22	52.4	34.978	0.000*
	Preterm	13	8.7	20	47.6		
Birth weight	<2.5 kg	14	9.3	26	61.9	55.077	0.000*
	2.5-3.0 kg	108	72.1	12	28.6		
	>3.0 kg	28	18.6	4	9.5		

*=Significant (p<0.05)

Table 4 summarises the descriptive statistics of foetal outcome variables and the result of Pearson's Chi-square test to compare the normotensive and preeclampsia groups. In the normotensive group, 97.4% (n=150) babies delivered were stable as none required NICU admission while 2.6% (n=4) pregnancies terminated due to intrauterine foetal death (IUFD). In the preeclampsia group, 8.7% (n=4) pregnancies culminated in IUFD while 17.39% (n=8) required NICU admission. The preeclampsia group had significantly poor foetal outcome as compared to the normotensive group (p<0.001). In the normotensive group, 8.7% deliveries (n=13 out of 150 live births) were preterm while 47.6% (n=20 out of 42 live births) deliveries were preterm in the preeclampsia group. In the normotensive group, 9.3% (n=14) babies delivered had low birth weight as compared to 61.9% (n=26) in the preeclampsia group. Both of these differences were statistically significant (p=0.000).

DISCUSSION

In the present study, the enrolled participants were categorized as normotensive or preeclampsia group depending on the diagnostic condition on the basis of regular recurrent investigation of the participants.

The blood pressure of the participants differed significantly in the normotensive and preeclampsia groups which is expected as it is the defining characteristic of the preeclampsia. The participants from preeclampsia group had significantly higher diastolic as well as systolic blood pressures. The mean arterial pressure (MAP) in the preeclampsia group was significantly higher than that of the normotensive group. The finding is in concordance with the results obtained by Upadhyay and Dayal.[10]

In the present study, MAP was found to be a more accurate predictor of prospective occurrence of preeclampsia than serum uric acid and salivary uric acid both. Cnossen et al found MAP to be a better indicator of PE than systolic or diastolic pressure alone.[11] Similar findings were reported by Walsh and Baxi and Zhu et al.[12,13]

The serum uric acid level came out to be an adequately accurate predictor of preeclampsia with a cutoff value of 5.18 mg/dl having an optimum sensitivity and specificity of 66.2% and 71.7% respectively. The positive predictive value (PPV) of this cut off was 88.7% while negative predictive value (NPV) was 38.8%. It could also discriminate between cases of severe and non-severe preeclampsia as reported by Singh et al and Madaan et al.[8,9]

Salivary uric acid has a strong correlation with the serum uric acid.[9] The present study also found a significant high positive correlation between these two measures. Analysis of ROC curve gave an AUC of greater than 0.5 but much lower than 1.[14] In our study, the salivary uric acid level was not found to be as reliable indicator of prospective preeclampsia as serum uric acid level.[15] The cut off value 4.86 mg/dl had a sensitivity of 70.8%, specificity of 45.7% and a PPV of 81.3%. In the study of Singh et al in 2019, the optimum cut off value of salivary uric acid was reported to be 3.350 mg/dl with 78% sensitivity and 73% specificity.[8] The comparable cut off of 3.32 mg/dl from the data of the present study had a sensitivity of 59.1% and a specificity of 52.2%.

The present study, thus, concurs with the study by Singh et al. that salivary acid can be a reliable predictor of preeclampsia. However, it differs in the cut off value of the salivary uric acid level. Another study be Madaan et al in 2022 reports the lowest best cut off value of salivary uric acid to predict preeclampsia to be 5.06 mg/dl with a diagnostic accuracy of 78.33%.[9]

Fetal outcome can be either stable, requiring neonatal intensive care unit (NICU) admission or might be intra-uterine fetal death (IUFD). While 2.6% participants from normotensive group experienced IUFD, the proportion was higher (8.7%) in the other group. The babies of none of the normotensive participants required NICU admission while 17.39% babies from the preeclampsia group needed NICU admission. Uzan et al also reported adverse fetal outcome as one of the major risks of preeclampsia.[2] Higher risk of NICU admission in neonates of mothers with PE was also reported by Mendola et al and Habli and others.[16,17] In respect of gestational age at delivery, 90.3% normotensive mothers delivered at term as compared to only 52.4% mothers who developed preeclampsia. Both the groups differed significantly in this regard.

The distribution of weight at birth revealed that the babies of 72.1% of normotensive mothers weighed between 2.5 kg to 3 kg while 9.3% delivered low birth weight babies (<2.5 kg). The percentage of low birth weight babies was significantly higher in case of participants with preeclampsia which reiterates the negative fetal outcomes in case of preeclampsia.[2]

CONCLUSION

In summary, salivary uric acid is a promising diagnostic predictor of preeclampsia in pregnant women by the virtue of being a non-invasive investigation and having good sensitivity and specificity. There is, however, a need of further large sample studies to arrive at a reliable cut off value for this investigation to obtain a practical role in clinical setting.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of GSVM Medical College, Kanpur (India)

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